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Editorial

Considerations of Risks Versus Benefits

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An evaluation of risks versus benefits from new products should be encouraged, even when dealing with agents which may cause cancer or malformations in laboratory animals, because there is evidence that safety thresholds exist even for such exposures. However, it is not easy to describe risk and benefit in comparable terms when they may involve generations to come and events in the future.

Risk versus benefit analysis regarding the exposure of man and his environment to new chemical, physical, or biological agents resulting from altered or new technological developments, has become a familiar phrase. It has been on the minds of scientists, public health officials or administrators, but has not resulted in technical or conceptual clarification regarding the requirements for satisfactory analysis. Different points of view on benefits to society and on willingness to take calculated risks can be heard. Individuals may be willing to take risks and enjoy the realization of having taken risks—in driving cars, flying planes, participating in certain sports, or by sticking to their pack of cigarettes a day.

Taking risks with the health of the unsuspecting public, however, is quite a different matter. The risks we shall deal with here are of the latter type, and it is up to those entrusted with safeguarding the public health to make risk/benefit evaluations for society and the environment on the basis of information available to them. Usually such information on potential hazards of newly developed products or substances is fragmentary and woefully inadequate. It is not only a matter of research funds or time until "complete safety evaluations" will be forthcoming but a profound question of how far such safety determinations can be attempted even with all the ingenuity of science at its disposal.

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Although it may appear as if two camps with closed lines regarding benefits or risks were confronting each other, this is not true. Experts on risks to man and his environment bring different arguments to the debate than do experts on benefits except in the area of drug development. Here risks and benefits focus on the same individual and he is often willing to take great risks where the alternative is the certainty of ill health or death. Under these conditions, risks to society as a whole are subjugated to considerations of the individual.

Alternatives

Some agreement has been seen in the evaluation of costs versus benefits for certain developments where, for instance, the dollar cost for installation of air cleaning equipment could be equated with the value of reduction of toxic components in the air. This was then compared to lower frequency of respiratory infections, improved visibility, or reduced deterioration of consumer products. A case was made for the replacement of the cheap pesticide DDT by a more expensive one which also required more frequent application and proved very hazardous in the field to man and beast. Other hoped-for developments in insect control focus on chemosterilants, which may also carry a definite risk. This, however, is reduced by combining them with specific insect sex attractants, thus avoiding at least elimination of harmless or beneficial insects. Other alternatives, like

the use of parasitic insects or pathogenic bacteria or viruses for insect control have been developed. The greatest promise for a satisfactory solution has recently come from development of interference with reproduction by alteration of the proportion of isomers of sex attractants, leading to a no-risk situation except for those natural predators that will find their food supply depleted. With such developments around the corner the use of DDT may decline in spite of the tremendous service that the chemical has given man in disease control, but even for those situations, development of resistance in the insects serving as disease vectors has required the use of alternative pesticides until resistance in the species has declined. Although these evaluations of the costs of changes in agricultural or public health practices can give us useful information, the risk of building up DDT in human adipose tissue to much higher levels has not so far been evaluated.

Benefits

In situations where risks to man or the environment may not exist, there may still be disagreement regarding the benefits to society. Rain or snow cloud seeding has been considered a low-risk task, but the practice has raised questions regarding the rights to clouds. Aided precipitation may deprive a neighboring area from getting its accustomed supply of rain. Alternatively, cloud seeding may serve a local farming population but not those that depend on tourist trade. These may not be real problems but benefit evaluation will have to take many subgroups of the population into consideration.

Announcements of benefits to be derived from new chemical developments often stress the value to the consumer: e.g., the availability of cheaper or better or more durable products; the contribution to improved health of the general population; better utilization of resources; or greater productivity of industry, greater employment of the work force or even improved balance of trade for the country. All these points are successfully documented.

Risks

To consider the risks, experts in different fields may want to be heard. The environmentalists will focus on damage to the environment, including the decline of many species most people hardly know by name, or on excess use or misuse of natural resources. The toxicologists may worry about acute toxicity, delayed toxicity, or may be concerned about the impact on the food chain and cumulative toxicity in order to determine the hazards to man. Except in situations of acute toxicity ending in death, an assessment of the dollar value of the risk is not usually attempted, because costs of morbidity or unhappiness with environmental changes (such as loss of beauty) are nearly impossible to assess. However, there is great merit in such dialogues on risks versus benefits when arguments are presented with utter conviction and sincerity on both sides.

When a conclusive evaluation of the risk still seems impossible, the temporary solution to the problem may lie in a carefully planned limitation of use of the product, with proper education in the handling of the material and attention to the correct means of disposal of the chemical. There might be information on the time span until a better product can be developed. This would appear preferable to taking no action until all the pieces on risk fit together or until a new product is developed for which a cleaner bill of health may be given. This may be misleading because, for reasons of its newness, fewer studies on potential risks will have been made.

Extrapolation to the Human Situation

An evaluation of the risk for man has even been difficult where epidemiological data could point a finger at a specific environmental or occupation exposure because it might have been impossible to confirm a cause-and-effect relationship from animal experiments. Differences in responses to exposure to toxic chemicals between man and laboratory animals have often been recorded and serve as warning that, in the evaluation of the risks from new chemicals, care has to be taken to plan experiments that may be useful for extrapolation of the data to man. Even so, some adverse health effects will still only be detected on human exposure—idiosyncrasies—but without too much risk for the general population. Animal experimentation can focus on serious health effects. Nevertheless, ototoxic effects, for instance, may be quite

serious but will not be detected following normal bioassay procedures.

When it is not possible to study health effects on man during the development of new chemical products and when animal experiments will not give all the information needed, it is important to be aware of this grey area for which no safety evaluation will be forthcoming. Few experiments have been carried out on exposure to stress, although stress has been studied together with exposure to environmental insults as affecting the health of the unborn, i.e., where abortions or malformations have been observed in animal studies. The effects of stress have been studied in many different situations, but no laboratory experiments have been carried out with the human suppressed reaction to stress, which has been shown to lead to many types of psychosomatic diseases (*1*). These conditions will not be mimicked in animal experiments, and allowance will have to be made for such commonly encountered situations superimposed on exposure to environmental toxicants.

Routine risk evaluation of a new chemical starts easily enough with an evaluation of chemical and physical data of relevance to potential hazards: e.g., volatility, water or lipid solubility, stability in the environment, or degradability by chemical or biological means. This information is supplemented with data on acute toxicity, subacute toxicity, and information on the reversibility of the adverse effects. Helpful information is sometimes obtained from a comparison of toxicity data from chemically closely related compounds. This evaluation by analogy, however, may go too far if it shows a lack of hazard or recommends a ban of the compound.

Chronic toxicity evaluation frequently cannot be based on acute toxicity data. Inert lipid-soluble compounds tend to accumulate in certain tissues and may exert delayed toxicity which would not be anticipated. Acutely toxic and reactive compounds may have a no-adverse-effect level at which, under continued exposure, toxicity may manifest itself by symptoms quite different from the symptoms of acute toxicity. For carcinogenesis, such observations have frequently been made.

Careless attempts to mimic conditions of human exposure in animals may lead to unexpected mistakes, because conditions may not have been equivalent. Thus inhalation of an aerosol in mice may give different deposition patterns and results than inhalation of the aerosol in man. Feeding a lipid-soluble chemical with the normal rodent diet may produce less absorption of the chemical than would occur with the usual human diet. By necessity, the greatest discrepancy, however, is the difference in dose required to produce a toxicologic effect in the limited number of exposed animals compared to the human population at risk.

Besides such anatomical differences of the tracheobronchial tree or the differences in diet, emphasis must be put on comparability of absorption, distribution in the organism, retention and elimination of the chemical to obtain the greatest degree of analogy in the risk evaluation, and possible explanations of species differences in observed response. Most critical is the comparability of metabolism of the compound which must be studied regarding all major or minor pathways, metabolic shunts, and the effects of administration of enzyme inducers (intercurrent exposures to pesticides, drugs, or food additives that may affect the enzymatic pathways). Close control of the animal colony regarding these factors may not allow any extrapolation to man, who may have developed preferential metabolic pathways due to exposure to some enzyme inducer or inhibitor. Carbon monoxide may serve as an example of an inhibitor. A detailed study of human as well as laboratory animal habits is quite essential.

The above points must be taken into consideration in the planning stage or at least in the evaluation of results. However, a very difficult problem lies in the determination of significance of negative findings, i.e., the extrapolation to a safe dose. Already in 1954, Barnes and Denz (*2*) grappled with this problem, determining the minimum number of animals required to control the risk of failing to observe an adverse effect. To detect with a degree of probability of 0.01 an adverse reaction occurring in 1% of the animals, one would require a group of no less than 455 animals. This requirement has hardly been followed for the reason that the cost of experiments would become prohibitive, particularly for studies of carcinogensis because of their long duration. Exposure to still lower dosage to reach the level of human exposure becomes unmanageable and costly and still will not yield data that would give any assurance of the safety of this exposure for the total population.

The difficulties in determining a "no-adverse-effect level" in animal experiments by extrapolation have been discussed repeatedly. Bliss (*3*) stated that the effect of low doses was qualitatively different from that of high doses. This problem has presented real difficulties regarding the acceptance of no-adverse-effect levels for carcinogenic chemicals when concepts borrowed from radiation carcinogenesis were transposed. These suggest that a single molecule might cause a permanent change which might, together with many similar events acting cumulatively over a lifetime, produce cancer. That this is not quite so could be shown by exposing animals to low doses of a carcinogen and allowing several months time before subsequent treatments with a promoter of carcinogenesis. When the carcinogenic response was no longer as expected, it was suggested that during the time interval many of the initiated cells had disappeared or could no longer respond (*4*).

Studying the events in carcinogenesis and mutagenesis goes further to prove that the reaction of carcinogens or mutagens with DNA are not irreversible events. They need not lead to the expression of mutations or cancer. Repair of genetic damage has been established for several species, from bacterial to human cells. Evidence came from studies on bacterial supersensitivity to radiation, the induction of mutator genes in bacteria (*5*) and from observations on patients with xeroderma pigmentosum (*6*) where sensitivity to sunlight resulted in skin cancers in exposed areas. These multiple cancers are due to inadequacy of the cellular DNA repair mechanisms. Such deficiencies can be induced by mutations or by exposure to a few chemicals which interfere with enzymatic activity (*7*) but these studies surely demonstrate that in the general population the irreversibility of a one-molecule event at the DNA level does not apply, and therefore that no-effect-thresholds must exist. It is true, of course, that exposure to chemicals that can block DNA repair mechanisms could present an extreme health hazard and must be effectively guarded against.

It should be realized that the heterogeneity of the human population and their health experiences during a lifetime present different circumstances for which the findings of toxicity in inbred strains of rodents or even random-bred animals do not allow reliable extrapolation. Genetic factors, as well as immunological, nutritional, enzymatic alterations and many other changes resulting from past or present injury to organs or tissues may contribute their share to enhance susceptibility to toxic agents. For many of these conditions, the persons thus afflicted are adequately prepared by knowing about their increased vulnerability and by attempting to protect themselves as long as the harmful exposure can be identified.

For newly developed chemicals, toxicity data will not necessarily alert the more susceptible groups of the increased risk. The tests do not even cover all potential adverse effects. The hope that adverse effects—such as allergic reactions—which are not evaluated by laboratory bioassay could be readily detected in man may be fulfilled, while the adverse effects relating to genetic or somatic debilities may not be detected as readily or before harm may become irreversible.

Interactions of environmental agents may have a qualitively or quantitively different adverse effect on man than each of the agents separately. For many chemicals the encounter need not be simultaneous, but even a time interval of several days may still allow such interactions. Some of these are of an antagonistic nature (*8*); many others are synergistic (*9*). From our point of view these synergistic interactions may be troublesome for the evaluation of environmental risks.

A familiar example of synergism can be taken from the field of flavors. It is well known that flavors change in quality on addition of common salt, but more so by addition of monosodium glutamate or the disodium salts of 5′-inosinic or 5′-guanylic acids or by maltol (*10*). A different kind of synergism is encountered by cigarette smokers where the chemicals responsible for the enhanced risk, particularly to lung cancer, have not been identified but where good evidence for synergism exists (*11*). In occupational cancer, synergism between carcinogenic polycyclic hydrocarbons and other components of crude oil has also been postulated to exist.

The effect of microsomal enzyme induction by environmental chemicals or drugs in altering the effectiveness or toxicity of drugs or chemicals has been studied in depth. However because of differences in rates of induction of several enzyme systems, some of them leading

to alternate pathways, it is not always possible to predict whether toxicity of a chemical will be reduced or enhanced, even if its metabolism is well studied and the active compound identified. For instance, metabolism by ring hydroxylation versus *N*-hydroxylation can be mentioned, with the former leading to innocuous products and the latter to potential carcinogens (*8*).

Synergism requires a certain concentration of the interacting components. In the field of carcinogenesis, when the promoter is present at too low a concentration no synergism is observed. However it is unfortunately not true that high enough concentrations of promoters are never encountered except under laboratory conditions—witness all those, for instance, for whom moderate smoking is not feasible.

Medical progress brings with it new procedures such as the use of immunosuppression, which has already produced an increased cancer risk in the recipients (*12*). Similarly, lengthening the life expectancy of man will probably result in an increased cancer risk, particularly when by synergistic action the latent period of cancer development will be shortened. Thus the aging population will have to look forward to a higher incidence of cancer as part of the price of longevity.

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